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(54) **Cytomodulating conjugates of members of specific binding pairs.**

(57) Novel conjugates are provided comprising a moiety capable of specifically binding to a target cell joined to a selective moiety for binding to an endogenous effector agent, capable of causing cell inactivation or cytotoxicity. Example of conjugates are a ligand for a surface membrane protein, e.g. IL-2 receptor, joined to a polysaccharide A or B antigen. The conjugates may be used to specifically destroy cells associated with a pathogenic condition.

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The field of this invention is cytomodulating conjugates of members of specific binding pairs and to therapeutics employing such cytomodulating compounds.

The immune system is our major defense against a wide variety of diseases. However, in many situations, the immune system appears to be unable to protect the host from disease or is aberrant and attacks the host, being unable to distinguish between self and non-self. In both situations, there is an interest in being able to modulate the immune system, either activating the immune system toward a particular target or inactivating the immune system to prevent attack of a target.

For the most part, success in preventing immune system attack has relied upon the total inhibition or suppression of the immune system. In this situation, the host becomes susceptible to a wide variety of opportunistic infections. Therefore, while achieving one goal, one must protect the host against pathogens, which can result in extended periods of hospitalization, maintenance by antibiotics with the resulting side effects, and the like. By contrast, it is believed that the immune system is normally capable of protecting the host from tumorigenesis. However, the substantial incidence of cancer is evidence of the inability of the immune system to maintain perfect surveillance. In this situation, there is an interest in being able to activate the immune system so as to increase its capability to attack cancer cells.

There is, therefore, an interest in providing for therapies, which can be specific for activating particular cells to be directed toward a specific target or inactivating specific cells which are directed to a specific target. In this way, one may selectively activate or inactivate cellular members of the immune system to achieve a therapeutic goal.

Lorberbaum et al., *J. Biol. Chem.* (1990) 265:18311-7 describe a polyethyleneglycol modified IL-2. Batra et al., *ibid* (1990) 265:15198-202 describe a fusion protein comprising a single chain antibody. Garrido et al., *Cancer Res.* (1990) 50:4227-32 describe bispecific antibodies to target human T-lymphocytes. Pullen et al., *Cell* (1990) 61:1365-74, describe the region of the T-cell receptor beta chain that interacts with the self-superantigen Mls-1A. Garrido et al., *J. Immunol* (1990) 144:2891-8 describe targeted cytotoxic cells. Junghans et al., *Cancer Res.* (1990) 50:1495-502 describe a humanized antibody to the IL-2 receptor. Schroeder et al., *Transplantation* (1990) 49:48-51 describe antimurine antibody formation following OKT3 therapy. Kaplan and Mazed, *Int. J. Artif. Organs* (1989) 12:79-804 describe *in vitro* removal of anti-A and anti-B antibodies with synthetic oligosaccharides. A review of blood groups antigens may be found in *FEMS Microbiol. Immunol.* (1989) 1:321-30.

Conjugates of selective binding moieties are

used to modulate immune response. The conjugates, referred to as "complexines" comprise a moiety which binds to a target cell receptor or receptor complex and a moiety which binds to an effector agent, endogenous to the host, which provides for cytomodulation, normally cytotoxicity. The complexine is administered to the host in amounts sufficient to provide for the desired prophylactic or therapeutic effect.

The present invention provides a method for inactivating a target cell in a mammalian host comprising said target cell and an endogenous cytotoxic effector system comprising at least one effector agent, said method comprising:

introducing a conjugate into said host in sufficient amount to substantially reduce the target cell population, wherein said conjugate is characterized by comprising a moiety specific for a surface membrane receptor joined to a selective moiety capable of binding to said effector system to form a cell inactivating complex, with the proviso that when said selective moiety binds to a T-cell, it binds to the T-cell receptor, wherein said effector system comprises (1) antibodies specific for said selective agent and an antibody dependent cytotoxic system comprising at least one effector agent or (2) a T-cell, whereby when said conjugate is bound to said target cell and said effector agent, said cell is inactivated. The selective moiety may be a blood group antigen or a superantigen. The selective moiety may bind to a cytotoxic T-cell. The moiety for said surface membrane protein may be a ligand for a cytokine surface membrane protein receptor of said target cell. The ligand may be IL-2.

The present invention also provides a method for inactivating a target cell in a mammalian host comprising said target cell, said method comprising:

introducing a conjugate into said host comprising an endogenous cellular effector system, comprising at least one effector agent, capable of inactivating said target cell, wherein said conjugate is characterized by comprising a ligand capable of binding to a surface membrane protein receptor joined to a selective moiety capable of binding to said effector agent to form a cell inactivating complex, wherein said selective moiety is a blood group antigen or at least a portion of a protein vaccine and said effector agent comprises an immunoglobulin, whereby when said conjugate is bound to said target cell and said effector agent, said cell is inactivated. The ligand may be a cytokine or an antibody for a cytokine receptor. The ligand may be IL-2.

The present invention also provides a composition comprising a ligand capable of binding to a surface membrane protein covalently joined to a blood group antigen or superantigen or at least a portion of a vaccine immunogen. The ligand in the composition may be IL-2 joined to a blood group antigen.

In accordance with the subject invention, methods and compositions are provided for therapeutic

treatment of a host, where the action of the immune system is modulated, so as to provide for prophylactic or therapeutic effect. The agent employs a conjugate having two moieties, each moiety having physiological activity. One moiety provides for binding to a target cell. The other moiety provides for interaction with a member of the immune system, whereby endogenous agents provide for the prophylactic or therapeutic effect. The conjugates may be as a result of chemical binding, either covalent or non-covalent, or a fusion protein by means of genetic engineering. Thus, the complexine components may be held together by means of a synthetic bridge, a peptide bridge, a membrane, e.g. liposome, polymer or particle, etc.

The conjugates are called "complexines," since they result in the formation of complexes with members of the immune system, which provide for modulation of the activity of a target cell. By administering the complexines to a host, the complexines will bind to a surface membrane protein or protein complex of the target cell, while also binding to endogenous effector agent present in the host. The endogenous effector agent results in an endogenous pathway which provides for inactivation or removal of the target cell from the host. For the most part, cytotoxicity is obtained, whereby the target cell is killed.

The moiety which binds to the target cell receptor may be any of a wide variety of molecules, including immunoglobulins, fragments thereof, including heavy chains, light chains, Fab, F(ab')₂, Fv, Fc, either monoclonal or polyclonal, and the like; anti-idiotypic antibodies, which simulate a ligand; ligands for receptors, such as the interleukins, 1-10, particularly -2, -4 and -6; molecules which bind to cluster designation surface membrane proteins, such as CD3, -4, -5, -8, -10, -15, -19, -69, etc.; growth factors, such as GM-CSF, G-CSF, M-CSF, EGF, TGF, TNF, interferons, etc.; molecules which bind to any of the members of the T-cell receptor, either the sub-units of T1 or T3; slg, molecules which bind to infectious agents etc.; molecule which bind to LPS, or other pathogenic cellular marker; molecules which bind to bacterial receptors, etc.; in the case of transplantation of organs, HLA molecules or fragments derived therefrom, derived from donor HLA antigens, particularly the variable region, while for bone marrow transplants the HLA molecules will be from the recipient antigens, etc.

The other moiety of the conjugate is a selective member, where the member directly or indirectly binds selectively to an effector system, comprising one or more effector agents endogenous to the host. By endogenous is intended an agent which is naturally present or may be safely administered to the host, e.g. antibodies, so as to be able to react with the selective members. The member may include an antigen to which the host has been previously sensitized or to which the host has natural antibodies, so as to have memory cells and/or specific soluble antibodies

in the blood stream, such as oligosaccharide A or B antigens, vaccine antigens (immunogens) which encounter antibodies due to a prior immune response, e.g. diphtheria or tetanus antitoxin, influenza virus hemagglutinin, HBs antigen, polio virus, rubella virus or measles virus antibodies, such as antibodies to DNA, RNA or ribonucleoprotein; for a T-cell response, tuberculin, HIV, particularly gp 120; a superantigen, such as toxins derived from *Staphylococcus* or other bacteria, e.g., SEC1, SEA, SBB, EXFT, TSST1, Mls, or minor histocompatibility antigens from mammalian cells. The superantigens bind to a substantial proportion of the V β chains of the T-cell receptor, T1. In all cases, one may use vicarious groups which provide the same function, e.g. binding. Of particular interest are anti-idiotypic antibodies or the variable regions thereof, which will mimic the selective moiety or bind to antibodies present in the host. The antibodies may interact with the members of the complement cascade or other cytotoxic agent, e.g. ADCC, to kill the target cell or the selection member may bind to a T-cell which provides a cytotoxic function.

The members of the conjugate may be polypeptides, saccharides, lipids, nucleic acids, or naturally occurring or synthetic organic molecules other than the molecules already described. The members of the conjugate may be joined directly or through a bridge of not more than about 50 members in the chain, usually not more than about 20 members in the chain, where the members of the chain may be carbon, nitrogen, oxygen, sulfur, phosphorous, and the like. Thus, various techniques may be used to join the two members of the conjugate, depending upon the nature of the members of the conjugate, the binding sites of the members of the conjugate, convenience, and the like. Functional groups which may be involved include esters, amides, ethers, phosphates, amino, hydroxy, thio, aldehyde, keto, and the like. The bridge may involve aliphatic, alicyclic, aromatic, or heterocyclic groups. A substantial literature exists for combining organic groups to provide for stable conjugates. Conjugates involving only proteins or glycoproteins can be chimeric or fusion recombinant molecules resulting from expression of ligated open reading frames of natural sequences, synthetic sequences, or combinations thereof.

Illustrative of complexines are IL-2 or CD69 binding protein individually linked to polysaccharide A and polysaccharide B antigen as a mixture, where the complexine comprises individual A and B molecules, although in some situations, it may be desirable to have more than one A or B molecule per conjugate to provide for higher avidity or activity or vary the *in vitro* solubility of the complex or for extended immune complexes and/or more than one ligand moiety per conjugate, for similar reasons. Since about 95% of individuals have natural anti-A and/or anti-B antibodies, the complexine will be effective in about 95% of individ-

uals. Thus, one could have a combination of IL-2, IL-4 and/or CD69 binding protein or combination of selective moieties e.g. A + B + vaccine Ag.

The multivalent complexine when administered intravenously would result in immune complexes of a size, which allows for solubility in the circulation and will bind to T-cells expressing the target surface membrane protein. If, one wishes to destroy activated T-cells which have a high level of IL-2 receptor or express CD69, the subject complexines will serve to bind via antibodies to the selective moiety to complement or other cytotoxic agent, such as ADCC cells, to substantially reduce the activated T-cell population. The binding of the immune complexes to the target cells will result in complement activation and/or opsonization resulting in target cell lysis. Other effector agents, include lymphocytes, or neutrophils, such as T-cells or K-cells, NK cells, monocytes, macrophages, basophils, eosinophils, mastocytes, erythrocytes, etc. By employing superantigen selective for cytotoxic T-cells, one may recruit such cells for their cytotoxic effect.

The subject compositions may be used for the treatment of a wide variety of pathologies, by varying the moiety for the target cell. Thus, treatments may include immunosuppression for organ transplantation, treatment for neoplasia, such as carcinomas, leukemias, lymphomas, sarcomas, melanomas, etc., autoimmune diseases, such as rheumatoid arthritis, multiple sclerosis, lupus, etc.; cellular pathogens; and the like.

One example is immune suppression associated with organ transplantation. In this situation, one would wish to inactivate or destroy T-cells which are active against the organ transplant. Thus, those T-cells which are activated and have high levels of IL-2 receptor or recognize the HLA antigen, may be selectively targeted for destruction by use of a complexine comprising one or more IL-2 ligands or binding portion thereof or other ligands, e.g. other interleukin, or one or more HLA antigens or the variable regions thereof of the organ donor. In the case of a bacterial infection, one may use a lectin or antibody specific for an epitopic site of the pathogen bonded to the A and/or B antigen to enhance the immune response to the pathogen.

The subject conjugates will for the most part be administered parenterally, particularly intravascularly, topically, as an aerosol, orally or the like, depending upon the particular organ, system or chamber to be treated. The amount of the conjugate which is administered will vary widely, depending upon the nature of the conjugate, the nature of the disease being treated, whether one or more administrations are to be made, the endogenous level of the effector or level stimulated by the complexine, the desired cytotoxic level, and the like. Thus, for each conjugate, one will determine empirically the level to be administered for

a particular indication. The conjugates may be administered in any convenient carrier, such as distilled water, phosphate buffered saline, saline, aqueous ethanol, blood derivative, or other conventional carrier. Other additives may be included, such as stabilizers, biocides, buffers, salt, and the like, these additives being conventional and used in conventional amounts.

The following examples are by way of above illustration and not by way of limitation.

EXPERIMENTAL

Example 1. Complexine with red blood group A antigen.

Blood-group A synthetic trisaccharides (8-azido-carbonyloctyl-derivatives of alphaGalNac1, 3-[alpha-Fuc 1,2]betaGal, derivatized to include a C-terminal amino group is conjugated to Interleukin 2 as follows:

I. Activation of Interleukin 2

1. 0.2 mg of (13 nmoles) of IL-2 is dissolved in 0.3 ml of 0.1 M sodium phosphate pH 7.5.
2. 2.3 mg N-Succinimidyl S-Acetyl thiolacetate is dissolved in 1 ML of DMSO.
3. 10 μ l of N Succinimidyl S-Acetyl thiolacetate is added to the IL-2 solution and the mixture is incubated at 25°C for 30 minutes.
4. The reaction mixture is passed through a G-25 column equilibrated with 0.1 M phosphate buffer pH 6.0. Free thiol groups are introduced by adding 100 μ l of 0.5 M hydroxylamine/0.05 M sodium phosphate pH 7.5 containing 0.025M EDTA to the IL2 Solution. The solution is stirred for 120 minutes at room temperature. The solution is passed through a G-25 column and free SH groups on IL-2 are obtained. Free SH groups are quantified using the Ellman's test, by measuring the absorbance at 412 nm.

II. Activation of Blood Group A Trisaccharide (A antigen) With Maleimido Group

1. A antigen (0.50 to 2 x molar excess of IL-2 is dissolved in 1.0 ml of 0.1 M sodium phosphate pH 7.5.
2. Succinimidyl N-Maleimido-6-aminocaproyl (2-nitro-4-sulfonic acid) phenyl ester. Na (MALSA-HNSA) (100 molar excess) is dissolved in 20 μ l of dimethyl sulfoxide (DMSO).
3. The reagent solution (2) is added to the A antigen solution and the mixture is incubated at 25°C for 1 hour.
4. The reaction is monitored by diluting 10 μ l of the reacting mixture into 1.0 mL of 0.01 M sodium phosphate, pH 7 at timed intervals. Each aliquot

is analyzed by reading the absorbance at 406 nm (A406) before and after addition of 50 μ l of 5 N NaOH. The percentage of active ester at any time is calculated using the formula: $[(A406(\text{NaOH}) - A406)/A406(\text{NaOH})] \times 100$. From the difference between the amount of ester at t_0 and at a time thereafter, the amount of ester used at that time is calculated. That corresponds to the amount of total amino group modified.

5. The reaction mixture is centrifuged briefly to remove excess of precipitated reagent and the supernatant is applied to a Sephadex G-25 column equilibrated in 0.1 M phosphate pH 6.0.

III. Conjugation

6. To maleimido-A antigen (in 0.1 M phosphate pH 6.0), is added IL-2-SH compound and allowed to stir at 4° C overnight. The final molar ratio of Mal- A antigen and IL-2-SH is adjusted from 0.2 to 5. The reaction mixture is then passed through Sephacryl- 200. The fractions having peaks at desired mol. weight ranges are collected.

Antigenic reactivity of the conjugate is tested by Western blot using anti-blood group antigen human serum and anti-IL2 monoclonal antibody.

C: Functional Assay of A-Complexine

In this experiment, it is determined whether the A-Complexine can be used to induce *in vitro* the specific killing of lymphocytes expressing a high affinity IL-2 receptor, when mixed with human serum containing anti-blood group A antibodies and complement. ^{51}Cr labelled CTL-L2 lymphocytes are incubated with A-Complexine (from 40 $\mu\text{g}/\text{ML}$ to 0.1 ng/mL). After 45 min. incubation at 37° C, human serum containing anti-blood group A antibodies (B group) is added at various dilutions and incubated for 30 minutes at 37° C; Rabbit complement is then added and incubated 1 hour at 37° C. The amount of ^{51}Cr released is then estimated and the percentage of specific cell lysis calculated. Significant lysis of CTL-L2 cells is observed after incubation with A-Complexine. The phenomenon is dose dependent (increased cytotoxicity, with higher amounts both of A-Complexine and anti-blood group A positive serum) and specific, as IL2-receptor negative cell lines (such as DA-1a mouse cells) are not killed under the same assay conditions. Furthermore, no significant cytotoxicity is observed when using human serum from a blood group AB or A individual.

HBs Complexine

A cyclical peptide derived from the amino-acid sequence (a.a. 139-147) of Hepatitis B virus surface antigen (HBsAg) and showing antigenic reactivity with polyclonal and monoclonal antibodies defining the a

epitope of HBsAg (HBs peptide) is used for conjugation with interleukin 2. The peptide sequence is: $\text{NH}_2\text{-Cys-Thr-Lys-Pro-Thr-Asp-Gly-Asn-Cys-Tyr-COOH}$. It is synthesized by solid phase method (Merrifield) using Fmoc chemistry. It is purified by HPLC. A disulfide bond is introduced between the two terminal cysteine residues by oxidation with potassium ferricyanide.

HBs peptide is conjugated to Interleukin 2 as follows:

I. Activation of Interleukin 2

1. 0.2 mg of (13 nmoles) of IL-2 is dissolved in 0.3 ml of 0.1 M sodium phosphate pH 7.5.
2. 2.3 mg N-Succinimidyl S-Acetyl thiolacetate is dissolved in 1 mL of DMSO.
3. 10 μ l of N-Succinimidyl S-Acetyl thiolacetate is added to the IL-2 solution and the mixture is incubated at 25° C for 30 minutes.
4. The reaction mixture is passed through a G-25 column equilibrated with 0.1 M phosphate buffer pH 6.0. Free thiol groups are introduced by adding 100 μ l of 0.5 M hydroxylamine/0.05 M sodium phosphate pH 7.5 containing 0.025 M EDTA to the IL-2 solution. The solution is stirred for 120 minutes at room temperature. The solution is passed through a G-25 column and free SH groups on IL-2 are obtained. Free SH groups are quantified using the Ellman's test, by measuring the absorbance at 412 nm.

II. Activation of HBs Peptide With Maleimido Group

1. HBs peptide (0.50 to 2 x molar excess of IL-2) is dissolved in DMSO at 10 mg/mL and diluted in 1.0 ml of 0.1 M sodium phosphate pH 7.5.
2. Succinimidyl N-Maleimido-6-aminocaproyl (2-nitro-4-sulfonic acid) phenyl ester. Na (MAL-SAC-HNSA) (100 molar excess) is dissolved in 20 μ l of N-N dimethyl sulfoxide (DMSO).
3. The reagent solution (2) is added to the HBs peptide solution and the mixture incubated at 25° C for 1 hour.
4. The reaction is monitored by diluting 10 μ l of the reaction mixture into 1.0 ML of 0.01 M sodium phosphate pH 7 at timed intervals. Each aliquot is analyzed by reading the absorbance at 406 nm (A406) before and after addition of 50 μ l of 5N NaOH. The percentage of active ester at any time is calculated using the formula: $[(A406(\text{NaOH}) - A406)/A406(\text{NaOH})] \times 100$. From the difference between the amount of ester present at t_0 and at a time thereafter, the amount of ester used at that time is calculated. That corresponds to the amount of total amino group modified.
5. The reaction mixture is centrifuged briefly to remove the excess of precipitated reagent and the

supernatant is applied to a Sephadex (G-25 column equilibrated in 0.1 M phosphate pH 6.0).

III. Conjugation

6. To maleimido-HBs peptide (in 0.1 M Phosphate pH 6.0) is added IL-2-SH compound and allowed to stir at 4° C overnight. The final molar ratio of Mal-HBs peptide and IL₂-SH are adjusted from 0.2 to 5. Finally the reaction mixture is passed through Sephacryl-200. The peaks at the desired mol. weight ranges are collected.

Antigenic reactivity of the conjugate is tested by Western blot using anti-HBs monoclonal antibody (A specific) and anti-IL-2 monoclonal antibody.

C: Functional Assay of HBs-Complexine:

In this experiment, it is determined whether the HBs-Complexine can be used to induce in vitro the specific killing of lymphocytes expressing a high affinity IL-2 receptor, when mixed with human serum containing anti-HBs antibodies and complement. ⁵¹Cr labelled CTL-L2 lymphocytes are incubated with HBs-Complexine (from 20 µg/mL to 0.1 ng/mL). After 45 min. incubation at 37 °C, human serum containing anti-HBs antibodies (collected from a patient vaccinated using Hevac B, Pasteur Vaccins and tested for anti-HBs antibodies by ELISA (Abbott Laboratories)) is added at various dilutions, incubated for 30 minutes at 37° C; Rabbit complement is then added and incubated 1 hour at 37 ° C. The amount of ⁵¹Cr released is then estimated and the percentage of specific cell lysis calculated. Significant lysis of CTL-L2 cells is observed after incubation with HBs-Complexine. The phenomenon is dose dependent: increased cytotoxicity is observed both with higher amounts of HBs-Complexine and anti-HBs positive serum. Cytotoxicity is specific, as IL-2 receptor negative cell lines (such as DA-1a mouse cells) are not killed under the same assay conditions. Furthermore, no significant cytotoxicity is observed when using human serum negative for anti-HBs antibodies.

In accordance with the subject invention, agents are provided which can specifically bind to a target cell, human, bacteria, virus infected or parasitic, via a specific binding ligand. Thus, agents can be selected which show a low affinity for cells which do not pair with the receptor complementary binding member. While using specific agents which interact with an endogenous effector molecule, one can achieve cytotoxicity toward the target cell following binding of the conjugate to the target cell. By employing agents for the ligand moiety, which do not induce a significant immune response, such as molecules which are substantially endogenous or have low immunogenicity, one can avoid an immune response and thus avoid having agents of the immune response destroy or in-

activate the therapeutic conjugate. In contrast, by taking advantage of the preexisting immune response against the selective moiety and because the ligand moiety remains functional, one can use the subject agents on a chronic basis.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

Claims

1. A conjugate for inactivating a target cell in a mammalian host which has an endogenous cytotoxic effector system at least one effector agent, said conjugate comprising a moiety specific for a surface membrane receptor joined to a selective moiety capable of binding to said effector system to form a cell inactivating complex, with the proviso that when said selective moiety binds to a T-cell, it binds to the T-cell receptor complex wherein said effector system comprises (1) antibodies specific for said selective agent and an antibody dependent cytotoxic system comprising at least one effector agent or (2) a T-cell, whereby when said conjugate is bound to said target cell and said effector agent, said target cell is inactivated.
2. A conjugate according to claim 1, wherein said selective moiety is a blood group antigen or a superantigen.
3. A conjugate according to claim 1, wherein said selective moiety binds to a cytotoxic T-cell.
4. A conjugate according to claim 1, wherein said moiety for said surface membrane protein is a ligand for a cytokine surface membrane protein receptor of said target cell.
5. A conjugate according to claim 4, wherein said ligand is IL-2.
6. A conjugate for inactivating a target cell in a mammalian host which has an endogenous cellular effector system, comprising at least one effector agent said conjugate comprising a ligand capable of binding to a surface membrane protein receptor joined to a selective moiety capable of binding to said effector agent to form a cell inactivating complex, wherein said selective moiety is a blood

group antigen or at least a portion of a protein vaccine

and wherein said effector agent comprises an immunoglobulin, whereby when said conjugate is bound to said target cell and said effector agent, said target cell is inactivated.

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7. A conjugate according to claim 6, wherein said ligand is a cytokine or an antibody for a cytokine receptor.

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8. A conjugate according to claim 7, wherein said ligand is IL-2.

9. A pharmaceutical comprising a conjugate according to any one of claims 1 to 8.

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10. A method of using a conjugate according to any one of claims 1 to 8 to prepare a medicament for inactivating a target cell in a mammalian host.

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11. A composition comprising a ligand capable of binding to a surface membrane protein covalently joined to a blood group antigen or superantigen or at least a portion of a vaccine immunogen.

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12. A composition according to claim 9, wherein said ligand is IL-2 joined to a blood group antigen.

13. A nucleotide sequence which encodes a conjugate according to any one of claims 1 to 8 where such conjugate is a protein.

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